10-31-03 #AF

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) (Large Entity)	Docket No. RLL-5.4DIV

In Re Application Of: ANAND et al.

Serial No.	Filing Date	Examiner	Group Art Unit
09/578,239	May 24, 2000	Sonya N. Wright	1626

Invention: 1-(4-ARYLPIPERAZIN-1-YL)-OMEGA -[N- (ALPHA,OMEGA -DICARBOXIMIDOL]-ALKANES URO-SELECTIVE ALPHA1-ADRENORECEPTOR BLOCKERS

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a response to the Office Action of May 30, 2003 (Date) above-identified application.

The requested extension is as follows (check time period desired):

☒ One month ☐ Two months ☐ Three months ☐ Four months ☐ Five months

from: September 30, 2003 (Date) until: October 30, 2003 (Date)

The fee for the extension of time is $110 and is to be paid as follows:

☐ A check in the amount of the fee is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-0912
A duplicate copy of this sheet is enclosed.

☒ If an additional extension of time is required, please consider this a petition therefor and charge any additional fees which may be required to Deposit Account No. 50-0912
A duplicate copy of this sheet is enclosed.

G. E. H. — *Signature*

Dated: October 30, 2003

George E. Heibel, PhD., Esq.
Reg. No. 42,648
Ranbaxy Pharmaceuticals Inc.
600 College Road East, Suite 2100
Princeton, New Jersey 08540

11/04/2003 AWONDAF1 00000022 500912 09578239
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cc:

I certify that this document and fee is being deposited on October 30, 2003 with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Michelle Morgan
Signature of Person Mailing Correspondence

Michelle M rgan
Typed or Printed Name of Person Mailing Correspondence

TRANSMITTAL OF APPEAL BRIEF (Large Entity)

Docket No. RLL-5.4DIV

In re Application Of: **ANAND et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
09/578,239	May 24, 2000	Sonya N. Wright	1626

Invention: **1-(4-ARYLPIPERAZIN-1-YL)-OMEGA - [N-(ALPHA,OMEGA-DICARBOXIMIDOL)]-ALKANES ALPHA1 -ADRENORECEPTOR BLOCKERS**

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on **July 30, 2003**

The fee for filing this Appeal Brief is: **$320.00**

☐ A check in the amount of the fee is enclosed.

☐ The Commissioner has already been authorized to charge fees in this application to a Deposit Account. A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **05-0912**
A duplicate copy of this sheet is enclosed.

Signature

Dated: **October 30, 2003**

George E. Heibel, PhD., Esq.
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Ranbaxy Pharmaceuticals Inc.
600 College Road East, Suite 2100
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I certify that this document and fee is being deposited on **October 30, 2003** with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Michelle Morgan

Signature of Person Mailing Correspondence

Michelle Morgan

Typed or Printed Name of Person Mailing Correspondence

cc:

IN THE BOARD OF APPEALS AND INTERFERENCES
OF THE UNITED STATES PATENT & TRADEMARK OFFICE

On Appeal of the Final Rejection
dated May 23, 2003 in the matter of:

Applicant:	ANAND et al.	
Application No.:	09/578,239	Examiner: Sonya N. Wright
Filing Date:	May 24, 2000	Group Art Unit: 1626
For:	1-(4-ARYLPIPERAZIN-1-YL)-ω-[N-(α,ω-DICARBOXIMIDOL)]-ALKANES USEFUL AS URO-SELECTIVE α_1-ADRENORECEPTOR BLOCKERS	

BRIEF ON APPEAL

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. Real Party in Interest

The real party in interest in this case is Ranbaxy Laboratories Limited, the Assignee of the present application, the assignment being recorded at Reel 010409, Frame 0988, recorded 11/12/1999 in the parent case, U.S. Patent Application Nos. 09/120,265 and 09/203,855.

2. Related Appeals and Interferences

There are no other appeals and/or interferences related to this case.

3. Status of Claims

Claims 44, 45, 48 and 49 are pending in the application

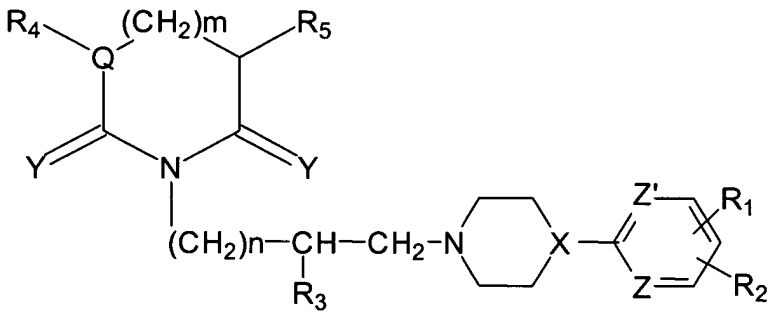
Claims 44, 45, 48 and 49 have been finally rejected in the application.

4. Status of Amendments

No amendment has been filed subsequent to the Final Office Action mailed May 30, 2003.

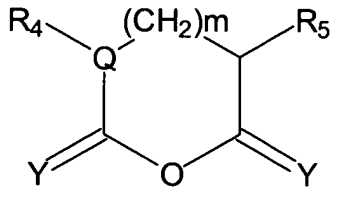
5. Summary of Invention

The present invention relates to processes for making compounds having the structure of Formula I, its pharmaceutically acceptable salts, enantiomers, diastereomers, or N-oxides.



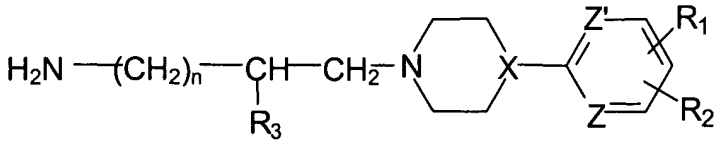
(I)

In the structure of Formula I, **Y** is O or S; **Q, Z** and **Z′** are independently CH; X is CH or N; **m**=0; **n**=0-4; $\mathbf{R_1}$, $\mathbf{R_2}$ are independently selected from: F, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; and R_3, R_4 and R_5 are independently H, $C_{1\text{-}3}$ alkyl, substituted or unsubstituted phenyl. The processes include reacting compounds having the structure of Formula VI′



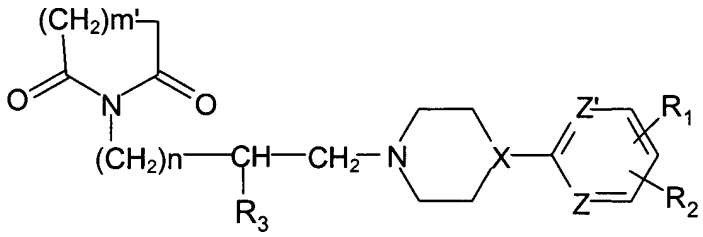
(VI')

with compounds having the structure of Formula V. This reaction can be carried out in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride to produce compounds of Formula I.



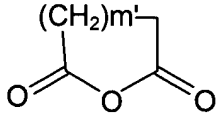
(V)

The present invention also relates to processes for making compounds having the structure of Formula II, its pharmaceutically acceptable salts, enantiomers, diasteromers, or N-oxides.



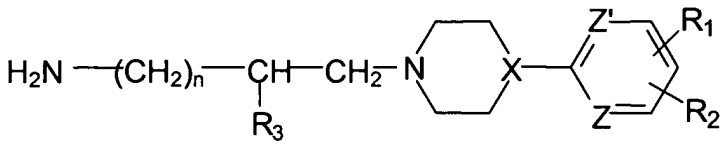
(II)

In the structure of Formula II, X is CH or N; Z and Z' are independently CH; n= 0-4; m' = 1; R_1, R_2 are independently selected from: F, Br, OCH_3, OC_2H_5, OCH_2CF_3, SCF_3, isopropyloxy, and cyclopropyl; and R_3 is independently H, C_{1-3} alkyl, substituted or unsubstituted phenyl. The processes include reacting compounds having the structure of Formula VI



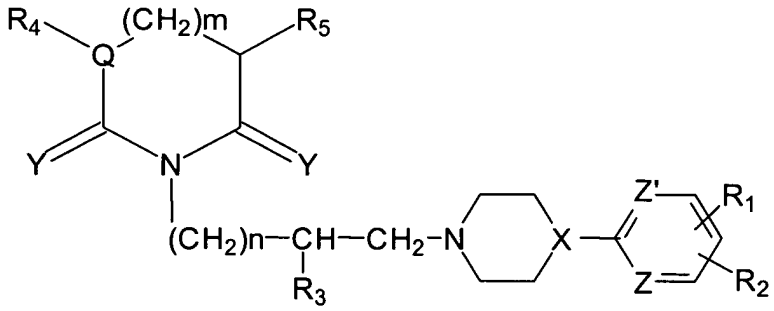
(VI)

with compounds having the structure of Formula V. This reaction can be carried out in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride to produce compounds of Formula I.



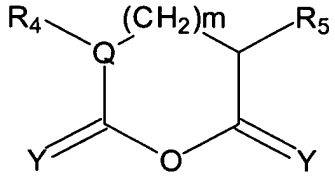
(V)

The present invention also relates to processes of making compounds having the structure of Formula I, its pharmaceutically acceptable salts, enantiomers, diastereomers, or N-oxides.



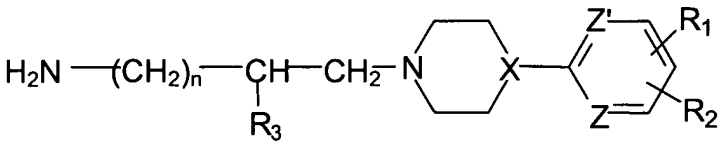
(I)

In the structure of Formula I, **Y** is O or S; **Q, Z** and **Z′** are independently CH; X is CH or N; **m**=1-3; **n**=0-4; $\mathbf{R_1}$, $\mathbf{R_2}$ are independently selected from: F, Cl, Br, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, C_2H_5, CF_3, isopropyloxy, and cyclopropyl; and R_3, R_4 and R_5 are independently H, $C_{1\text{-}3}$ alkyl, substituted or unsubstituted phenyl. The processes include reacting compounds having the structure of Formula VI′



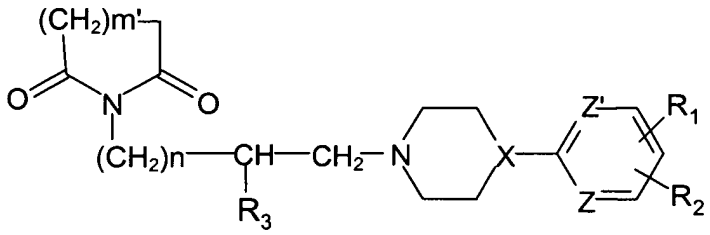
(VI')

with compounds having the structure of Formula V. The reaction can be carried out in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride to produce compounds of Formula I.



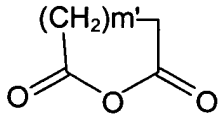
(V)

Finally, the present invention relates to processes for making compounds having the structure of Formula II, its pharmaceutically acceptable salts, enantiomers, diasteromers, or N-oxides.



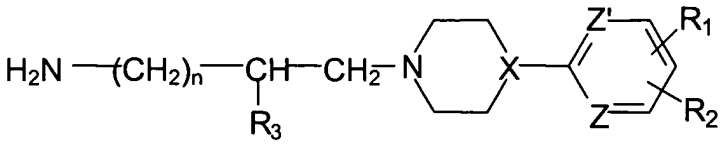
(II)

In the structure of Formula II, X is CH or N; Z and Z' are independently CH; n= 0-4; m' = 2-4; R_1, R_2 are independently selected from: F, Cl, Br, OC_2H_5, OCH_2CF_3, SCF_3, CH_3, isopropyloxy, and cyclopropyl; and R_3 is independently H, C_{1-3} alkyl, substituted or unsubstituted phenyl. The processes include reacting compounds having the structure of Formula VI



(VI)

with compounds having the structure of Formula V. The reaction can be carried out in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride to produce compounds of Formula II.



(V)

6. Issues

Claims 44, 45, 48 and 49 are rejected under 35 U.S.C. §112, First Paragraph.

7. Grouping of Claims

All the claims appealed herein stand or fall together.

8. Argument

The rejection of claims 44, 45, 48 and 49 under 35 U.S.C. §112, First Paragraph is improper.

Claims 44, 45, 48 and 49 have been rejected as lacking support in the written description for reciting "in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride." Applicants respectfully submit that the claims 44, 45, 48 and 49 do in fact meet the requirements of 35 U.S.C. §112, First Paragraph, namely that

> "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

.In issuing a rejection based on a lack of written description, the Examiner bears a burden, as set forth in the MPEP § 2163.04:

> "The examiner must set forth express findings of fact which support the lack of written description conclusion... These findings must...b) establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed....the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 262 (C.C.P.A. 1976)" MPEP § 2163.04 (emphasis added)

This is entirely consistent with the pronouncements of the Courts on the written description requirement. "Precisely how close [to the claimed invention] the description must come to comply with §112 must be left to a case-by-case development." In re Smith, 458 F.2d 1389, 1395 (C.C.P.A. 1972). To date, this burden set forth in the MPEP and by the Courts has not been met by the Examiner.

Applicants respectfully submit that one of ordinary skill in the art, at the time of the filing of the invention, would have been reasonably apprised that applicants were in possession of the invention claimed in pending claims 44, 45, 48 and 49. See Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375 (Fed. Cir. 1983)).

In their Amendment and Response to Office Action, received by the Office on January 15, 2002, applicants amended claims 44 and 45 to recite the phrase "pyridine at reflux temperature followed by reflux in the presence of acetic anhydride." The Examiner's response, in paper number 9, was a final rejection of the claim, in part, because "Applicants have not shown description for the phrase 'pyridine at reflux temperature followed by reflux in the presence of acetic anhydride.'" (Paper No. 9, page 2).

Upon filing their Amendment and Response to Final Office Action, received by the Office on June 18, 2002, applicants pointed out that "the phrase 'pyridine at reflux temperature followed by reflux in the presence of acetic anydride' finds support in the example of the application as filed on page 16, at lines 6-7, Scheme-II." (page 4). In fact, the cited portion of applicants' specification reads in its entirety as follows:

> "Scheme-II: 1-amino-3-[4-(4-fluorophenyl)piperazin-1-yl]propane (0.700 g, 2.95 mmol) and succinic anhydride (0.295 g, 2,95 mmol) were refluxed in pyridine (10 ml) for 10 hours. Acetic anhydride (2 ml, excess) was added and the mixture was further refluxed for 5 hours." This procedure, after workup and purification, led to the isolation of Compound No. 1." (emphasis added).

The Examiner has asserted that "the phrase [regarding the reflux steps at issue] is included in a specific example, ... therefore the specification does not support the step [at issue] as being useful in the preparation of ALL compounds of claims 44, 45, 48 and 49." (Office Action, Paper No. 19, page 3; underlined emphasis added, capitalized emphasis in original). The Examiner's position seems to be that since the phrase at issue find support in the language of a specific example, it "therefore" does not support the process as applied to the scope of claims 44, 45, 48 and 49. Applicants disagree with the logical, legal and technical merits of that position..

Viewing the general description of the process of this conversion (Scheme II, page 11), and the example on page 16, lines 5-11 pertinent to this conversion, one of ordinary skill in the art would conclude that each of the compounds of claims 44, 45, 48 and 49 could be prepared in this way, and that this was expressed by applicants at the time of filing. That is, any compound within the scope of the pending claims "can also be prepared by condensation of the piperazines of Formula V with the anhydrides of Formula IV." (page 11, lines 3-5) One of ordinary skill in the art would then look to the examples for further guidance as to the particular teachings of applicants' specification, and would

then find that a particular piperazine (that is, 1-amino-3[4-(4-fluorophenyl)piperazin-1-yl]propane) and a particular anhydride (that is, succinic anhydride) were refluxed in pyridine for an extended period, and then acetic anhydride was added and the mixture further refluxed for another period. One of ordinary skill in the art would understand that this reaction, taking place "in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride" represents one general set of reaction conditions for the transformation described in Scheme II. The conclusion would not be that since the example provided a single working example, this was the only compound which could be transformed this way.

In fact, there is simply no reason why one of ordinary skill in the art would conclude that a reaction between another piperazine and another anhydride could not proceed according to the claim. The claimed process parameters involve reagents that are generally useful for such transformations (pyridine and acetic anhydride). Further, applicants expressly contemplate that "the reaction temperature and duration of reaction may be adjusted according to the desired needs" (page 13, lines 3-4).

In fact, the prior art under discussion in this prosecution discloses that these reactions may be carried out using these claimed reagents. For example, Khadilkar et al., in the first paragraph on page 530, discloses preparation of 1-[3-(4-(4-methylphenyl)-1-piperazinyl)propyl]-2,5-pyrrolidinedione, HCl using compound 7d and succinic anhydride, which were "refluxed in dry pyridine....Acetic anhydride... was added and the mixture was further refluxed..." (emphasis added). Similarly, Wu et al., in the last full paragraph in the left column on page 881, discloses preparation of N-[ω-(4-phenyl-1-piperazinyl)alkyl]cyclic imides by reflux in dry pyridine, followed by refluxing in acetic acid (i.e., Ac_2O). Thus, it is clear that one of ordinary skill in the art would

have understood applicants to have been in possession of the subject matter of the invention at the time of the filing of the application.

In the most recent mailing from the Office, a Final Rejection of the pending claims for the reason of this appeal (Paper No. 19), the Examiner applied the Wands factors to the rejection in this case. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, although the rejection was initially presented as an issue of lack of written description, in this most recent paper, the analysis has taken on the guise of an issue of enablement. Although applicants submit that the appeal should continue to be analysed in terms of written description, applicants here address the Examiner's characterization of the Wands enablement factors as follows:

1) Nature of the invention: Applicants are in general agreement with the Examiner as to the nature of the invention, as being drawn to a process for preparing compounds of Formula I, comprising reacting compounds of Formula VI' with compounds of Formula V in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride. However, it is noted that the invention is also drawn to the preparation of compounds of Formula II, comprising reacting compounds of Formula VI with compounds of Formula V in pyridine at reflux temperature followed by reflux in the presence of acetic anhydride.
2) State of the Prior Art: Applicants agree that the prior art does not directly state that any of the compounds of Formula I can be prepared by the instant process. This statement is made by applicants' application alone. However, the prior art cited in applicants' specification, and specifically the prior art of record in this prosecution, and mentioned in applicants' Response to Office Action Mailed December 19, 2002, page 9 (i.e., Khadilkar et al. *J. Ind. Chem. Soc.*, v. VLXII, 1986, pp 529-530; and Wu et al., *J. Med. Chem.*, v. 12, 1969, pp. 876-881) does indicate the generality of the cited reaction conditions, as set forth above.
3) Level of Ordinary Skill in the Art: The Examiner's characterization of the level of ordinary skill in the art is vague ("high"), and highly conclusory with respect to the objective enablement requirement. By stating that "[a]pplicants' specification does not enable the public to prepare all of the compounds of Formula I by the instant process," the Examiner has attempted to force a legal conclusion without considering the facts, and without taking up the burden of setting forth a reasonable explanation as to why [she] believes that the scope of protection provided by that claim is not adequately enabled..." In re Wright, 999 F.2d 1557 (Fed. Cir. 1993) (citing In re Marzocchi, 439 F.2d 220, 223 (C.C.P.A. 1971)).

4) Level of Predictability in the Art: The Examiner's characterization of the art is vague ("highly unpredictable"), and not based on any evidence. Further, by requiring "guidance that is applicable to all possible compounds of Formula I," the Examiner misstates the applicable legal standard that is required of applicants' patent specification. "The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP §2164.01 (citations omitted). Guidance as to every embodiment of applicants' disclosure is not required.
5) Amount of Direction and Guidance Provided by the Inventor: Again, the Examiner's conclusory statements ("limited guidance") simply do not amount to a finding of any facts with respect to this issue.
6) Existence of Working Examples: The Examiner admits that an example of the claimed process is provided. The law does not require any particular number of examples. "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP §2164.02. The Examiner has provided none of the facts and evidence required.
7) Breadth of Claims: Regardless of the scope of the claims, the Examiner has put forth no reasons why one of ordinary skill would not be able to practice the invention as claimed across its entire scope.
8) Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure: Here again, the Examiner makes only conclusory statements which do not provide any facts or evidence upon which to base any conclusions for this factor. The "numerous amount of modifications to perform in order to obtain comounds of Formula I as claimed" are nowhere discussed or clarified. There is no basis presented for any of the statements with respect to this factor.

In summary, the Examiner has not provided a factual basis for any of the conclusions presented with respect to the Wands factors, which are relevant to an enablement inquiry, nor with respect to the written description rejection initially presented. The law makes it clear that a description as filed is presumed to be adequate with respect to the written description requirement of 35 U.S.C. §112, First Paragraph, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., In re Marzocchi, 439 F.2d 220, 224 (C.C.P.A. 1971). Thus, it is clear that here, one of ordinary skill in the art would have understood that applicants have enabled the claimed method for the entire scope of the claims.

In light of the foregoing, Applicants submit that the claims are supported by the disclosure as filed, and all of the requirements of 35 U.S.C. §112, first paragraph have been adequately met. Therefore, the rejection of Claims 44, 45, 48 and 49 should be withdrawn and the claims should be allowed.

Respectfully submitted,
RANBAXY LABORATORIES LIMITED

By: _____
George E. Heibel, Ph.D., Esq.
Reg. No. 42,648

Date: October 30, 2003

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